Citation:

Takachi R, Inoue M, Ishihara J, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, Tsubono Y, Tsugane S; JPHC Study Group. Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. *Am J Epidemiol.* 2008 ;167(1):59-70.

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Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the associations between fruit and vegetable consumption and risk of total cancer and CVD in the same Japanese population.

Inclusion Criteria:

- Registered Japanese inhabitants from 11 public health center areas.
- Age: 40-59y (cohort I); 40-69 y (cohort II)
- 77,891 subjects (35,909 men, 41,982 women), including 3,230 with cancer (636 gastric cancer, 598 colorectal cancer, 397 lung cancer, 233 breast cancer, 193 liver cancer, 1,173 other cancers) and 1,386 with CVD (227 myocardial infarction, 1,159 stroke), were included.

Exclusion Criteria:

- Two public health center areas (Tokyo and Osaka) were excluded from the present analysis because either cancer or CVD incidence data were not available.
- CVD cases with a death certificate or self-report only, without confirmation by medical records, were excluded. Subjects who did not complete the diet part of the questionnaire and those with a past history of cancer or coronary heart disease and/or stroke.
- 4,098 who reported extreme total energy intake (lower and upper 2.5 percentiles, 883 and 3,981 kcal/day, respectively) were excluded.

Description of Study Protocol:

Recruitment

- The Japan Public Health Center-based Prospective Study was conducted on two cohorts, one initiated in 1990 (cohort I) and the other in 1993 (cohort II).
- During 1995–1998, a validated food frequency questionnaire was administered in nine areas to 77,891 men and women aged 45–74 years. During as many as 459,320 person years of follow-up until the end of 2002, 3,230 cancer cases and 1,386 CVD cases were identified.

Design: Prospective Cohort Study

- In this prospective cohort study, surveys of the cohort participants by self-administered questionnaire were conducted twice, the first in 1990 (cohort I) and 1993 (cohort II) and the second in 1995 (cohort I) and 1998 (cohort II).
- The second survey questionnaire included more comprehensive information on food intake frequency than the first, the second survey was used as the starting point to assess dietary exposure in the present study.
- The questionnaire also included other items on medical history and lifestyle factors, such as smoking and alcohol drinking. The remaining 114,865 subjects at the starting point were eligible as the study population after we excluded the 1,807 persons who had died, moved out of a study area, or were lost to follow-up before the starting point.
- A total of 91,103 subjects (42,708 men, 48,395 women) responded, yielding a response rate of 79.3 percent, and were included in the present study.
- Subjects in cohort I were followed from 1995, and subjects in cohort II were followed from 1998, until December 31, 2002.

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- According to the SAS PHREG procedure, hazard ratios and 95 percent confidence intervals were calculated for the categories of energy-adjusted fruit and vegetable consumption in quartiles for men and women combined, with the lowest consumption category as the reference, by using Cox proportional hazards models and adjusting for potential confounding variables
- Initial analyses by adjusting for gender, age at the starting point (5-year groups), and study area (nine public health center areas) was performed.
- In the multivariate model, further adjusted for smoking status (never, past, and current), alcohol consumption (none, occasional, 1–149, 150–299, 300–449, and >450 g of ethanol/week), body mass index in kg/m2 (<19, 19–22.9, 23–26.9, and>27), physical activity in metabolic equivalent task-hours/day (<30, 30–34.9, 35–39.9, and >40), quartile of total energy intake, current medication status (hypertension, hyperlipidemia, diabetes mellitus), daily vitamin supplement use, and screening examination (blood pressure, chest radiograph, gastric photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, colonoscopy for men and women, mammography, Papanicolaou smear for women).
- Linear associations were assessed by using the median values of fruit and/or vegetable intake for each quartile.
- Subgroup analyses was performed according to gender and smoking status (‘‘never’’ as nonsmoker and ‘‘past’’ and ‘‘current smoker’’ as ever smoker), age (<60 or>60 years), cohort (I or II), body mass index (<19 or 19–26.9 or _27 kg/m2), and alcohol intake (<150 or >150 g ethanol/week). In this paper, all p values are two sided, and statistical significance was determined at the $p < 0.05$ level.

Data Collection Summary:

Timing of Measurements

First in 1990 (cohort I) and 1993 (cohort II) and the second in 1995 (cohort I) and 1998 (cohort II). Food frequency questionnaire was administered in 9 areas.

Dependent Variables

- Hazard ratio for CVD: diagnoses of myocardial infarction according to the criteria of the MONICA project and diagnoses of stroke by computer tomographic scan and/or magnetic resonance imaging according to the criteria of the National Survey of Stroke.

- Hazard ratio for cancer: cases of cancer were coded according to the International Classification of Diseases for Oncology, Third Edition.

Independent Variables

- Fruit and vegetable intake measured using food frequency questionnaire
- The FFQ included 138 food and beverage items with standard portions/units and nine frequency categories.

Control Variables

- Age
- Sex
- BMI
- Alcohol intake
- Smoking
- Dietary intake
- Energy intake
- Physical activity
- Vitamin use

Description of Actual Data Sample:

Initial N: 114,865 subjects

Attrition (final N): 91,103 subjects (42,708 men, 48,395 women)

Age: Cohort I: 40-59y; Cohort II: 40-69 y

Ethnicity: Asian (Japanese)

Other relevant demographics:

Anthropometrics: Body mass index ≥27 kg/m^2 (%y)

Location: Japan Public Health Center

Summary of Results:

Key Findings

- Higher consumption of fruit, but not vegetables, was associated with significantly lower risk of CVD: multivariate hazard ratios for the highest versus lowest quartiles of intake were 0.81 (95% confidence interval (CI): 0.67, 0.97; trend p = 0.01) for fruit and 0.97 (95% CI: 0.82, 1.15; trend p = 0.66) for vegetables.
- Consumption of fruit or vegetables was not associated with decreased risk of total cancer: corresponding hazard ratios were 1.02 (95% CI: 0.90, 1.14; trend p = 0.95) for fruit and 0.94 (95% CI: 0.84, 1.05; trend p =0.16) for vegetables.
- Total fruit and vegetable intake by the subjects ranged from a median value of 186 g/day in the lowest quartile to 733 g/day in the highest quartile.
- Both men and women whose fruit and vegetable consumption was higher were less likely to be ever smokers or heavy drinkers, and they were more likely to use vitamin supplements and have undergone various screening examinations.
- A significant inverse association was found between fruit consumption and risk of CVD, but not between vegetable intake and risk of CVD
- The only specific fruit or vegetable item significantly inversely associated with CVD risk was citrus fruits.
- No specific fruit or vegetable was significantly associated with risk of total cancer.
- Gender showed a significant inverse trend between fruit consumption and risk of CVD among women only.
- Smoking status showed no association between fruit or vegetable intake and CVD risk among ever smokers, but a significant inverse association was found between fruit consumption (not for vegetables) and CVD risk among nonsmokers.
- Higher fruit consumption was associated with lower risk of CVD but that neither fruit nor vegetable consumption was associated with cancer risk.
- No association was found between fruit or vegetable consumption and cancer risk for ever smokers or nonsmokers.
- The results suggest that the apparent gender differences in the association between fruit intake and CVD are attributable

in large part to the differences in the association by smoking status and the higher prevalence of ever smokers among men (65.3 percent) than among women (6.3 percent).

- CVD risk for women was significantly inversely associated with total fruit and vegetable consumption (multivariate hazard ratio (HR) of highest quartiles versus the lowest = 0.73, 95 percent CI: 0.56, 0.95; trend p = 0.02) and with fruit.
- Consumption (HR =0.78, 95 percent CI: 0.60, 1.01; trend p =0.06), and we found a nonsignificant, but inverse association with vegetable consumption (HR = 0.81, 95 percent CI: 0.63, 1.05; trend p =0.14).
- Citrus fruits was the only specific food group significantly inversely associated with CVD risk for both men (HR = 0.76, 95 percent CI: 0.61, 0.94; trend p =0.03) and women (HR =0.77, 95 percent CI: 0.59, 1.00; trend p = 0.06). No other individual food groups were associated with risk of cancer for men or women.
- The multivariate hazard ratios for the highest versus the lowest decile of consumption were 0.81 (95 percent CI: 0.61, 1.08) for fruit and CVD (trend p = 0.01), 0.87 (95 percent CI: 0.68, 1.13) for vegetables and CVD (trend p = 0.44), 1.07 (95 percent CI: 0.89, 1.27) for fruit and cancer (trend p = 0.57), and 1.02 (95 percent CI: 0.85, 1.21) for vegetables and cancer (trend p =0.32).

Author Conclusion:

In conclusion, the results of this population-based prospective cohort study in Japan suggest a protective association between fruit consumption and risk of CVD and no association between fruit or vegetable consumption and risk of total cancer.

Reviewer Comments:

Authors note the following limitations:

- *Validity of FFQ for fruit and vegetable intake was moderate at best (r = 0.34 - 0.57)*
- *Stroke accounted for most (84%) of the CVD, thereby limiting comparability of the findings in this study and previous studies in Western populations, in which coronary heart disease accounted for the majority of CVD*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes

1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	N/A
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes

4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes

	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
	7.7.	Were the measurements conducted consistently across groups?	N/A
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes